Nivolumab Use for First-Line Management of Hepatocellular Carcinoma: Results of a Real-World Cohort of Patients

Pramod Gaudel, MD; Ghulam Rehman Mohyuddin, MD; and January Fields-Meehan, MD

Background: Patients with advanced hepatocellular carcinoma (HCC) have a poor prognosis. First-line multikinase inhibitors like sorafenib and lenvatinib are poorly tolerated and have low response rates. Several clinical trials have shown tolerability and efficacy of immunotherapy in this setting. The objective of this retrospective study was to determine the outcomes of front-line nivolumab in a frail real-world population.

Observations: In this retrospective study conducted between January 2016 and December 2019, 14 men (median age, 63.5 years; range, 58-72 years) with HCC received nivolumab as front-line systemic therapy. Only 2 patients had a response to immunotherapy (14.3%), of which 1 patient had a complete response (7.1%). The median progression-free survival was 4 months and median overall survival was 8 months. Incidence of grade 3 or higher toxicity was 35%.

Conclusions: In our small, real-world cohort of patients receiving immunotherapy as front-line systemic treatment for HCC, outcomes were poor with front-line immunotherapy.

Hepatocellular carcinoma (HCC) has a poor prognosis and remains an important cause of cancer-related morbidity and mortality.[1,2] Potentially curative interventions include surgical resection, radiofrequency ablation, and liver transplantation. However, the majority of patients are not eligible for these procedures because they are diagnosed at an advanced stage, when locoregional therapies are much more limited.[3,4] Although the kinase inhibitors sorafenib and lenvatinib are approved as first-line systemic treatment, at the US Department of Veterans Affairs (VA) Kansas City VA Medical Center (KCVAMC) in Missouri, nivolumab was used instead because of concerns for the tolerability of the kinase inhibitors. Locoregional therapies, resection, and transplantation options were either not appropriate or had been exhausted for these patients. The objective of this retrospective study was to determine the outcomes of those veteran patients in a small cohort.

METHODS

The KCVAMC Institutional Review Board approved this retrospective chart review. Patients were selected from pharmacy records at KCVAMC. We identified all patients with a diagnosis of HCC who received nivolumab from January 2016 to December 2019. We then included only the patients that had nivolumab in the front-line setting for our final analysis. At the time of initiation of treatment, all patients were informed that immunotherapy was not approved for front-line treatment, but available evidence suggested that it would be easier to tolerate than sorafenib or lenvatinib. These patients were determined to be either ineligible for sorafenib or lenvatinib therapy or expected to tolerate it poorly, and hence they consented to the use of nivolumab. Tumor response and progression were assessed by the investigator according to iRECIST (Immune Response Evaluation Criteria in Solid Tumors) criteria.[5] Data were obtained from retrospective health record review.

RESULTS

Fourteen men received nivolumab in the front-line systemic therapy setting from January 2016 to December 2019 at KCVAMC. The median age was 63.5 years (range, 58-72 years), and the median Eastern Cooperative Oncology Group score was 1. The Table highlights patient characteristics.

Of the 14 patients included in the review, 2 patients had a response to nivolumab (14.3%) and 1 patient had a complete response (7.1%). The median duration of immunotherapy was 4.5 months. Immunotherapy was discontinued due to disease progression in 10 patients and toxicity in 3 patients.

The median progression-free survival (PFS) from initiation of immunotherapy was 4 months; median overall survival (OS) was 8 months. The median time from

Pramod Gaudel and **Ghulam Rehman Mohyuddin** are Hematology-Oncology Fellow Physicians, both in the Department of Internal Medicine at The University of Kansas Medical Center in Westwood. **January Fields-Meehan** is an Attending Physician in the Department of Hematology and Medical Oncology at the Kansas City Veterans Affairs Medical Center in Missouri.
Correspondence: Pramod Gaudel (pgaudel@kumc.edu)

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TABLE Patient Demographics

Characteristics	Results
Age, median (range), y	63.5 (58-72)
Male sex, No. (%)	14 (100)
Child-Pugh score, No. (%) A B	 9 (64.2) 5 (35.8)
ECOG functional status, median	1
Causes of liver cancer, No. (%) Hepatitis C Nonalcoholic fatty liver Unknown	 10 (71.4) 2 (14.3) 2 (14.3)
AFP-elevated, No. (%)	12 (85.8)
Biopsy proven, No. (%)	6 (42.9)
Locoregional disease at time of initiation, No. (%)	13 (92.9)
Prior receipt of locoregional therapies, No. (%) TACE Y-90 Microwave ablation Combination	9 (64.3) 6 (42.9) 1 (7.1) 1 (7.1) 1 (7.1)

Abbreviations: AFP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization; Y-90, yttrium-90.

diagnosis to survival was 41 months. Only 1 patient received a second-line treatment.

Incidence of grade 3 or higher toxicity was 35%. Three deaths resulted from autoimmune hepatitis (grade 5 toxicity), as well as 1 grade 3 skin toxicity, and 1 grade 4 liver toxicity.

DISCUSSION

Immunotherapy has shown promise in patients with HCC based on the results of the KEYNOTE-224 and Checkmate-040 studies,[6,7] which led to an accelerated US Food and Drug Administration approval of nivolumab and pembrolizumab for HCC following failure of first-line sorafenib.[8,9]

Several clinical trials are evaluating front-line immunotherapy for HCC. The Checkmate 459 study demonstrated the median OS to be 16.4 months for nivolumab vs 14.7 months for sorafenib, a difference that was not statistically significant. However, tolerability of nivolumab was better than it was for sorafenib, thus positioning it as a potentially attractive first-line option.[10] The GO30140 study evaluated atezolizumab and bevacizumab vs atezolizumab with results positive for a survival benefit in favor of combination.[11] This combination of atezolizumab and bevacizumab vs sorafenib also has been evaluated in the phase 3 IMbrave150 trial. Results from this trial show statistically significant improvement in the coprimary endpoints of OS and PFS in patients who were treated with atezolizumab and bevacizumab when compared with those who were treated with sorafenib. The median OS had not been reached for atezolizumab and bevacizumab vs 13.2 months for patients randomized to sorafenib, with a higher PFS and response rate also noted with combination treatment.[12]

The results from our study differed from the previous studies and raise concern for the applicability of these trials to a real-world population. For example, both the GO30140 and IMbrave150 excluded patients with untreated varices.[11,12] Both IMbrave150 and Checkmate 459 limited enrollment only to patients with a Child-Pugh A score for liver disease; 36% of the KCVAMC patients had a Child-Pugh B score. Three patients (21.4%) were homeless, 6 patients (42.8%) had substance abuse history and 5 patients (35.7%) had mental illness. Several psychosocial factors present in our patients, such as substance abuse, mental illness, and homelessness, would have excluded them from clinical trials. Our small cohort of patients, thus, represents a frail real-world population due to multiple medical and psychosocial comorbidities. Real-world experience with immunotherapy as second-line therapy after treatment with sorafenib has been reported, but this is the first reported real-world experience of immunotherapy in the front-line setting for HCC.[13,14]

Large differences in sociodemographic status and health status exist between the veteran population and typical clinical trial populations. Veterans are predominantly male and older than a clinical trial population. Veterans are more likely to belong to a minority group, more likely to have lower level education and more likely to be poor than a clinical trial population. They are more likely to have poorer health status with higher number of medical conditions and psychosocial conditions.[15]

Limitations

We acknowledge several limitations to our study, such as the small number of patients and the retrospective single center nature of this study. Patients were older men with multiple psychosocial comorbitities like mental illness, substance abuse, and homelessness. This cohort may not represent the non-VA population, but is an excellent representation of a frail, real-world veteran population.

CONCLUSIONS

Despite clinical trials showing the promise of immunotherapy as an attractive front-line systemic treatment option for HCC, our results show poor outcomes in a frail real-world population. In a cohort of patients who received immunotherapy as a front-line systemic treatment for HCC, results were poor with a response rate of 14.3%, a median PFS of 4 months, and a median OS of 8 months. We noted a significantly higher number of adverse effects, including 21% incidence of grade 5 hepatotoxicity. There remains an urgent need to develop more effective and safer therapies for this patient population as well as validation from larger real-world studies.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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